REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133. The outstanding office action is non-final because the finality of the previous office action was withdrawn pursuant to filing an RCE under 37 CFR 1.114.

Status of the Claims

Pending claims

Claims 31 to 43, 51, and 55 to 57 are pending.

Claims added in the instant amendment

Claims 58 to 63 are added. Thus, after entry of the instant amendment, claims 31 to 43, 51, and 55 to 63, will be pending and under consideration.

Outstanding Rejections

Claims 31 to 43, 51, and 55 to 57 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lavanchy *et al.* (J. Clinical Laboratory Analysis (1996) 10:269-76), Lee *et al.* (Transfusion (1995) 35:845-49), Rosa *et al.* (J. Virol. Methods (1995) 219:219-32), and Wang *et al.* (U.S. Patent No. 5,106,726 A).

Claims 31 to 43, 51, and 55 to 57 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shah *et al.* (U.S. Patent No. 5,705,330 A), Wang *et al.* (U.S. Patent No. 5,106,726 A), and Lambert S. (US. Patent No. 5,164,299 A).

Claims 32, 34, and 51 were rejected under 35 U.S.C. §112, second paragraph.

Claims 36-43, 56, and 57 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1 to 8 of U.S. Patent No. 6,379,886 B1.

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Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the amended claims. For example, the basis for the amendment of claims 31 and 36 is given in page 2, line 35 to page 3, line 38. Support for diagnostic reagents having a solid phase comprising a microtiter plate or a test tube, can be found, inter alia, on page 2, lines 25 to 26. Support for diagnostic reagents using a genetic recombinant HCV antigen having a molecular weight of 10,000 or more and a conjugated HCV antigen which comprises a HCV antigen conjugated with a carrier protein and having a molecular weight of less than 10,000, can be found, inter alia, on page 4, lines 1 to 13. Support for diagnostic reagents using a synthetic peptide having a molecular weight of 1,000 to 5,000, can be found, inter alia, on page 3, lines 7 to 23.

Accordingly, no new matter is added by the instant amendment.

Restriction Requirement

Applicants thank the Examiner for reconsidering the Restriction Requirement and rejoining claims 36 to 43, 56 and 57 to elected Group I, drawn to a diagnostic agent for HCV infection comprising, inter alia, a nonstructural region and synthesized HCV antigens comprising structural and nonstructural HCV peptide proteins of core NS4 and NS5, wherein the recombinant HCV antigen is directly sensitized onto the solid phase.

Issues under 35 U.S.C. §103(a)

Lavanchy, Lee, Rosa, Wang

The rejection of claims 31 to 43, 51, and 55 to 57, under 35 U.S.C. §103(a) as allegedly unpatentable over Lavanchy *et al.*, J. Clinical Laboratory Analysis (1996) 10:269-276, (hereinafter "Lavanchy"), Lee *et al.*, Transfusion (1995) 35:845-849 (hereinafter "Lee"), Rosa *et al.*, J. Virol. Methods (1995) 219:219-232 (hereinafter "Rosa"); and Wang *et al.*, U.S. Patent No. 5,106,726 A (hereinafter "Wang") is maintained for reasons of record.

A *prima facie* case of obviousness requires that three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. As presented below, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

The amended claims

After entry of the instant amendment, claim 31 is drawn to diagnostic reagents for hepatitis C virus (HCV) infection comprising a solid phase sensitized with (a) a genetic recombinant HCV antigen having a molecular weight of 10,000 or more and (b) conjugated HCV antigens comprising (i) a first HCV antigen conjugated with a carrier protein; and (ii) a second HCV antigen conjugated with a carrier protein; wherein each of the first HCV antigen and the second HCV antigen has a molecular weight of less than 10,000.

After entry of the instant amendment, claim 36 is drawn to diagnostic reagents for hepatitis C virus (HCV) infection comprising a solid phase sensitized with (a) a genetic recombinant HCV antigen having a molecular weight of 10,000 or more and (b) one or more conjugated HCV antigens, wherein the conjugated HCV antigen comprises a HCV antigen conjugated with a carrier protein and has a molecular weight of less than 10,000.

Lavanchy

Lavanchy neither teaches nor suggests any conjugated HCV antigen, e.g., an HCV peptide conjugated with a carrier protein. Because no conjugated HCV antigens are taught, Lavanchy also does not teach or suggest a combination of conjugated HCV antigen and a genetic recombinant HCV antigen.

The Office Action mailed June 15, 2004, noted that Lavanchy does not "... conjugate the antigens with BSA"; see paragraph 4, spanning pages 2 to 3, of that OA. Lavanchy specifically states "[i]n this study, we evaluated a new third-generation anti-HCV screening assay [their so-[illegible] of unrelated proteins" (emphasis added) (see page 269, second paragraph of the introduction section). Thus, the Lavanchy reference is defective in that, inter alia, it does not teach or suggest a solid phase sensitized with any conjugated HCV antigen, or, a solid phase sensitized with both conjugated HCV antigen and (one or more) non-conjugated HCV antigens.

Lavanchy provided data that demonstrated, and they concluded, that the tested Cobas Core Anti-HCV EIA assay "proved very useful for routine testing" (see, e.g., page 275, last paragraph). Accordingly, Lavanchy provides no motivation to modify the Cobas Core Anti-HCV EIA assay.

Lee

Lee does not cure the defect(s) in Lavanchy because, inter alia, it also neither teaches nor suggests a conjugated HCV antigen, e.g., an HCV peptide conjugated with a carrier protein. Lee describes a study that directly compared new third-generation HCV antigen detection assays with older (second generation assays). Unconjugated recombinant HCV antigens were used; see, e.g., Materials and Methods, "anti-HCV testing", spanning pages 845 and 846. None of the assays studied in Lee used any conjugated HCV antigen.

Furthermore, Lee concluded that the newer assays were very effective in detecting the presence of HCV antigen in blood samples. Accordingly, Lee provides no motivation to modify the tested hepatitis C assays.

Lee also does not teach or suggest a reagent of claim 31 or 36 of the present application. Lee does not teach or suggest a combination of a genetic recombinant HCV antigen and (one or more) conjugated HCV antigens, wherein the conjugated HCV antigen comprises a HCV antigen conjugated with a carrier protein. Further, Lee is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a

molecular weight of less than 10,000. In particular, it is entirely silent about the combination recited in claim 31 or 36.

Rosa

Rosa also does not cure the defect(s) in Lavanchy because, inter alia, it does not teach or suggest a conjugated HCV antigen, e.g., an HCV peptide conjugated with a carrier protein. Rosa also does not teach a solid phase sensitized with both conjugated HCV antigen and (one or more) non-conjugated HCV antigens.

Rosa describes a prototype ELISA for serodiagnosis of HCV. This assay uses a combination of a synthetic NS4-NS5 chimeric antigen and a recombinant core-NS3 chimeric antigen (see, e.g., last paragraph of the introduction section, page 220). However, no carrier proteins are used. Thus, Rosa does not teach or suggest use of HCV peptide conjugated with a carrier protein.

Furthermore, Rosa concluded that its chimeric peptides showed "excellent reactivity in an ELISA format" (see abstract, page 219). Accordingly, Rosa provides no motivation to modify the HCV antigens used in its assays.

In fact, Rosa actually teaches away from use of anything but minimal HCV epitopes, noting "[t]he use of short synthetic peptides to present minimal epitopes should be helpful in excluding the amino acid sequences that may be responsible for low specificity due to cross-reactivity with antibodies directed against other viral proteins" (see page 230 of Rosa).

Rosa does not teach or suggest a reagent of claim 31 or 36 of the present application. Rosa does not teach or suggest a combination of a genetic recombinant HCV antigen and (one or more) conjugated HCV antigens, wherein the conjugated HCV antigen comprises a HCV antigen conjugated with a carrier protein. Furthermore, Rosa is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000. In particular, it is entirely silent about the combination recited in claim 31 or 36.

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Wang

Wang does not cure the defect(s) in Lavanchy because, inter alia, it does not teach or suggest use of a solid phase sensitized with both genetic recombinant HCV antigen and (one or more) conjugated HCV antigens. Further, Wang is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000.

Wang is directed to methods for the detection in body fluids of antibodies to hepatitis C virus (HCV), including ELISAs and other forms of immunoassay procedures. Another embodiment of Wang is directed to methods for generating high titer antibodies using, inter alia, free, conjugated or polymeric forms of HCV antigens (see, e.g., last sentence of the abstract):

> The present invention also relates to a method for generating high titer antibodies to HCV in healthy mammals, including humans, by the use of compositions containing these synthetic peptides, analogues or mixtures thereof, in a free, conjugated or polymeric form as key components in synthetic vaccines for the prevention of non-A non-B hepatitis (NANBH).

In the OA of June 15, 2004, the Patent Office noted that Wang in columns 34 and 35, describes a method for conjugating HCV antigen with BSA, and coating an erythrocyte or some solid particle with the conjugated antigen; and that Wang concluded that this conjugated antigen is good for both quantitative and qualitative detection of antibodies to HCV (see page 3, paragraph no. 7, of the OA). Example 4, of Wang states (column 36, lines 18 to 33):

> One mL thoroughly washed erythrocytes, gelatin particles, or polystyrene latex particles are coated with the HCV peptide mixture, or conjugates thereof at an effective concentration. The peptide mixture, or conjugates thereof, coated cells or particles are then incubated with serially diluted serum samples in the wells of a 96-well U-shaped microplate or on a slide. After being left at room temperature for about an hour, or a few minutes in the case of latex particle based microagglutination, the settled agglutination pattern on the bottom of each well or on the slide is read; and the highest dilution showing a positive reaction is recorded.
>
> This is a one-step assay which can be used for both qualitative and quantitative detection of antibodies to HCV in specimens including sera or biofluids.

Thus, Wang teaches particles coated with an HCV peptide mixture or conjugates thereof. However, Wang does not teach or suggest the use of the specifically claimed combination of a conjugated HCV antigen and a genetic recombinant HCV antigen.

Furthermore, as noted above, neither Lavanchy, Rosa or Lee teach or suggest use of the combination of a conjugated HCV antigen and a genetic recombinant HCV antigen. Thus, Wang does not cure the defect(s) in Lavanchy, Rosa or Lee.

As noted above, none of the cited references Wang, Lavanchy, Rosa or Lee could have provided any motivation to the skilled artisan to modify any of the assays used in their studies or described therein. None of the cited references Wang, Lavanchy, Rosa or Lee provided any motivation to combine all or part of any additional assays. In fact, all of the cited references Wang, Lavanchy, Rosa and Lee concluded the assays studied or described therein were very effective – thus, providing no motivation for modification or combination. Applicants respectfully reiterate that none of the cited references Wang, Lavanchy, Rosa or Lee alone or in combination teach or suggest the (amended) claimed invention comprising use of the combination of a conjugated HCV antigen and a genetic recombinant HCV antigen. Further, Wang, Lavanchy, Rosa or Lee alone or in combination are silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000.

Accordingly, because none of the cited references Wang, Lavanchy, Rosa or Lee alone or in any combination teach or suggest the claimed invention (after entry of the instant amendment), a *prima facie* case of nonobviousness has not been made, and this rejection under section 103 can be properly withdrawn.

Shah, Wang, Lambert

Claims 31 to 43, 51, and 55 to 57 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shah *et al.* (U.S. Patent No. 5,705,330 A), Wang *et al.* (U.S. Patent No. 5,106,726 A), and Lambert S. (US. Patent No. 5,164,299 A), for reasons set forth on pages 5 to 6, paragraphs 17 to 25.

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Shah neither teaches nor suggests any conjugated HCV antigen, e.g., an HCV peptide conjugated with a carrier protein. Because no conjugated HCV antigens are taught, Shah also does not teach or suggest a combination of a conjugated HCV antigen and a genetic recombinant HCV antigen. Further, Shah is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000.

The Patent Office confirms this, noting that "Shah et al. also do not teach to conjugate the synthetic HCV antigen peptides to BSA before they are mobilized onto a solid support" (see page 6, paragraph 20, of the instant OA). In fact, Shah neither teaches nor suggests conjugating any HCV antigen, whether recombinant or synthetic.

Wang

Wang does not cure the defect(s) in Shah because, inter alia, it does not teach or suggest use of a combination of a conjugated HCV antigen and a genetic recombinant HCV antigen, as required by the amended claims. Further, Wang is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000. Wang is discussed in detail, above.

Lambert

Lambert does not cure the defect(s) in Shah because, inter alia, it does not teach or suggest use of a combination of a conjugated HCV antigen and a genetic recombinant HCV antigen, as required by the amended claims.

As noted by the Office (see paragraph 22, page 6, of the instant OA), Lambert teaches that a mixture of conjugated and unconjugated antigens in a certain proportion provides an enhanced assay performance; e.g., see abstract of Lambert:

> In a solid phase homogeneous or heterogeneous assay for detection or quantitation of an analyte in a biological fluid, use of a combination of conjugated and unconjugated reagent(s) immobilized on the solid phase provides enhanced assay performance.

Lambert only refers to hepatitis C virus (HCV) when generally discussing what agents can be detected by use of its assays, e.g., in column 3, lines 9 to 28:

> It is contemplated that the present invention may be applied to the detection of many different types of analytes for which there are specific binding partners. ... In particular, the methods of this invention are particularly well suited to the detection of antibodies which occur in response to exposure or infection with an etiological agent. Representative of such agents are the causative agents of hepatitis infections, such as hepatitis viruses A, B and C (non-A non-B), and retroviruses, herpes viruses, bacteria, fungi, chlamydia, rickettsia, and mycoplasma.

Example 1 of Lambert describes conjugating recombinant Hepatitis B core antigen to a solid phase (see columns 6 to 8). However, Lambert does not teach or suggest the use of a combination of a conjugated HCV antigen and a genetic recombinant HCV antigen of this invention. Further, Lambert is silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000.

Furthermore, none of the cited references Shah, Wang or Lambert provided any motivation to combine all or part of any additional assays. In fact, all of the cited references Shah, Wang and Lambert concluded the assays studied or described therein were very effective – thus, providing no motivation for modification or combination. Applicants respectfully reiterate that none of the cited references Shah, Wang or Lambert alone or in combination teach or suggest the (amended) claimed invention comprising use of the combination of a conjugated HCV antigen and a genetic recombinant HCV antigen.

Further, Shah, Wang and Lambert are silent that the genetic recombinant HCV antigen has a molecular weight of 10,000 or more and a HCV antigen of the conjugated HCV antigen has a molecular weight of less than 10,000.

Accordingly, because none of the cited references Shah, Wang or Lambert alone or in any combination teach or suggest the claimed invention (after entry of the instant amendment), a

prima facie case of nonobviousness has not been made, and this rejection under section 103 can be properly withdrawn.

Issues under 35 U.S.C. §112, second paragraph

Claims 32, 34, and 51 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The instant amendment addresses the Office's concerns.

Rejections Under Obviousness-Type Double Patenting

Claims 36 to 43, 56, and 57 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1 to 8 of U.S. Patent No. 6,379,886 B1.

1. A diagnostic reagent for detecting hepatitis C virus (HCV) infection comprising a solid phase to which three or more different HCV antigen-carrier protein conjugates are bound, wherein:

the carrier protein and HCV antigen are present in each conjugate at a ratio of about 1:3 to 1:20 (carrier protein:hepatitis C virus antigen),

each HCV antigen-protein conjugate has only one type of HCV antigen bound to it, and

each HCV antigen is from an antigen selected from the group consisting of core antigen, NS3 antigen, NS4 antigen and NS5 antigen.

2. A diagnostic reagent for hepatitis C virus (HCV) infection comprising a solid phase to which three or more different HCV antigen components are bound, wherein:

at least one of the antigen components is from an antigen selected from the group consisting of core antigen, NS4 antigen and the NS5 antigen and is attached to a carrier protein to form a HCV antigen-protein conjugate,

the bound carrier protein and HCV antigen are present in each component at a ratio of about 1:3 to 1:20 (carrier protein:hepatitis C virus antigen),

the HCV antigen-protein conjugate has only one type of HCV antigen bound to it, and

each HCV antigen component is from an HCV antigen selected from the group consisting of core antigen, NS3 antigen, NS4 antigen and NS5 antigen.

3. The diagnostic reagent for hepatitis C virus infection of claim 1 or 2, wherein each of the antigens of the three or more antigen-carrier protein conjugates has one or more different epitopes having HCV antigenic activity.

4. The diagnostic reagent for hepatitis C virus infection of claim 1 or 2, wherein the carrier protein is selected from the group consisting of bovine serum albumin (BSA), ovalbumin and hemocyanin.

5. The diagnostic reagent for hepatitis C virus infection of claim 1, wherein the carrier protein is selected from the group consisting of BSA, ovalbumin and hemocyanin.

6. The diagnostic reagent for hepatitis C virus infection of claim 1 or 2 wherein the solid phase is carrier particles.

7. The diagnostic reagent for hepatitis C virus infection of claim 6, wherein the carrier particles are hydrophobic particles.

8. The diagnostic reagent for hepatitis C virus infection of claim 7, wherein the hydrophobic particles are polystyrene latex.

Applicants elect to hold this issue in abeyance until such time claims are held allowable.

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CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §103(a) and 35 U.S.C. §112, second paragraph. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 322732000401. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Dated: December 12, 2005

Respectfully submitted,

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